REMARKS

I. Status of the Claims

Claims 21-38 and 44-61 are currently pending; claims 1-20 and 39-43 have been previously canceled because the Office considers these claims directed to a different invention. Upon entry of this amendment, claim 46 is amended without prejudice or disclaimer.

II. Claim Rejections under 35 U.S.C. §112, Second Paragraph

Claims 26 and 46 are said to be indefinite because the metes and bounds of the phrase "a symptom" are said to be unclear. The Office Action also asserts that the specification does not provide a standard for ascertaining what "symptom to monitor." The Office Action specifically contends that claims 26 and 46 broadly encompasses immune disorders, including those for which symptoms are undefined and that the phrase is thus indefinite. For the reasons that follow, Applicants disagree.

The key inquiry in determining whether claims are definite is whether "'those skilled in the art would understand what is claimed when the claims are read in light of the specification." (MPEP 2173.02, citing Orthokinetics, Inc. v. Safety Travel Chairs, Inc., 806 F.2d 1565, 1576, 1 USPQ2d, 1081, 1088 (Fed. Cir. 1986). It is also noted that the MPEP emphasizes that the claims need only define the subject matter with a reasonable degree of particularity and distinctiveness (MPEP 2173.02, emphasis in original).

The Office, however, in stating "that the term 'immune disorder' include[s] diseases that [are] not listed by Applicant [sic] and metes and bounds of 'a symptom' of said non-listed diseases are unclear" appears to set a much a higher standard, apparently taking the position that Applicants must define what is meant by "a symptom" for all known immune disorders for claims 26 and 46 to be definite. Such a standard, however, exceeds that required by the courts and the MPEP, as symptoms of immune diseases were known based upon general knowledge in the art and the disclosures in the specification. Such a requirement, moreover, is unfair, as Applicants cannot reasonably be expected to list symptoms for all known immune disorders.

According to MPEP 2173.02, a correct analysis of the standard for definiteness involves a consideration of several factors, including:

(1) the claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made;

(2) the teachings of the prior art; and

(3) the content of the particular application disclosure.

With respect to the first factor, it is submitted that the term "symptom" is well known in the art. Webster's New Collegiate Dictionary, for example, defines "symptom" as "something that indicates the presence of disease or physical disturbance," or as "subjective evidence of disease or physical disturbance" (Webster's New Collegiate Dictionary, G. & C. Merriam Co., 1977, p. 1181). Stedman's Medical Dictionary provides a similar definition, defining a "symptom" as "[a]ny morbid phenomenon or departure from the normal in structure, function, or sensation, experienced by the patient and indicative of disease" (Stedman's Medical Dictionary, 26th edition, Williams and Wilkins, Philadelphia, 1995, page 1718).

With respect to the second factor, that particular symptoms associated with various immune disorders were known in the art is evidenced from the discussion in a number of the references listed in the two tables below that discuss administering human IL-10 to ameliorate a variety of symptoms associated with immune disorders, including use in clinical trials. Although not all the references listed below were filed prior to the priority date of the instant application, many were. The Office Action also appears to acknowledge that symptoms were known in the art, stating that "The examiner agrees that . . . symptoms associated with various immune diseases are known in the art" (Office Action, page 3, 5th paragraph).

Finally, with respect to the third factor, although the Office Action at page 2 states that "applicant only disclosed the symptoms of *several* specific diseases", Applicants in fact set forth in considerable detail in the last response specific sections of the specification that describe exemplary symptoms for 19 different disorders. The Office's apparent requirement that Applicants exhaustively catalog the symptoms associated with all immune disorders imposes an impractical burden on Applicants. More importantly, such a burden exceeds the standard for enablement as set forth above.

So for all the foregoing reasons, it is submitted that claims 26 and 46 are definite and that this ground of rejection should be withdrawn.

Claim 46 is rejected for reciting to an "immune disorder" rather than an "inflammatory response." This claim has been amended to maintain proper antecedent basis.

III. Claim Rejections under 35 U.S.C. §112, First Paragraph

Claims 21-38, 44-61 are rejected under 35 U.S.C. §112, first paragraph because the specification is said not to enable one of ordinary skill in the art to practice the claimed invention without undue experimentation. The Office Action in general reiterates the three major rationales set forth in the previous Office Action to support this assertion, namely that: 1) the specification only provides in vitro examples, which are said not to correlate with the current claims that encompass in vivo treatment methods (paragraph bridging pages 3-4), 2) the specification lacks adequate guidance on how to assess treatment efficacy (first full paragraph on page 5), and 3) the specification does not enable prophylactic treatment methods (second full paragraph on page 5). For the reasons that follow, Applications disagree with each of these assertions.

With respect to the first assertion, the appropriate standard for evaluating whether in vitro examples correlate with claims to in vivo treatment methods was set forth in the last response. As noted in that response, the courts have emphasized that in vitro examples need only reasonably correlate with the claimed in vivo methods. As pointed out in the prior response, the Federal Circuit has held, for instance, that:

> [A] rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence. (*Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985); see also MPEP 2164.02.)

The Federal Circuit in the same case also stated that:

> [I]n vitro results with respect to the particular pharmacological activity are *generally predictive of in vivo test results*, i.e., there is a reasonable correlation therebetween. (*Id.*; emphasis added).

Despite the foregoing view that in vitro results are generally predictive of in vivo test results, the Office Action nonetheless takes the position that the numerous in vitro experiments described in the application do not correlate with the claimed in vivo methods. Applicants disagree with this conclusion and submit that the in vitro test results correlate with the claimed methods for several reasons.

First , to reiterate a point made in the last response, the numerous examples presented in the application demonstrate that treatment of different types of immune cells with rhesus CMV IL-10 (rhCMV IL-10) resulted in a *decrease* in the concentration of molecules (e.g., various cytokines and Class I and Class II MHC proteins) known to be *causative agents* of immune disorders. Moreover, addition of rhesus CMV IL-10 resulted in an *increase* in the concentration of *protective molecules* (e.g., HLA-G) known to protect against immune disorders. These results by themselves are sufficient in themselves for one of skill in the art to reasonably conclude that administering rhCMV IL-10 could be effective in vivo.

Secondly, that such results are indeed sufficient to enable the currently claimed methods is supported by issuance of U.S. Patents directed to the treatment of certain diseases using human IL-10 which are based upon in vitro results similar to those described in the current application. The following table illustrates the close parallels between the in vitro studies reported in two U.S. patents for the treatment of disease with human IL-10 and the in vitro results with rhCMV IL-10 described in the current application:

U.S. Patent	In Vitro Results Reported in U.S. Patent	Related In Vitro Experiments and Results from Current Application
US 5,770,190	Culturing cells in presence of human IL-10 in general tended to cause a decrease in cell proliferation (cols. 11-13) Administering IL-10 to cultured human PBMCs inhibited production of a number of cytokines, including TNF-alpha, GM-CSF, IL-1alpha, and IL-6 (col. 14)	Administration of rhCMV IL-10 to PBMCs from rhesus monkeys or humans resulted in marked inhibition of PBMC proliferation (example 2). Treatment of PBMCs or monocytes with rhCMV IL-10 inhibited synthesis of TNF-alpha (examples 6 and 8), GM-CSF (example 10), IL-1alpha (example 12) and IL-6 (example 14)
US 5,883,976	Administering human or viral IL-10 to cultured PBMCs inhibited the production of IFN-gamma, TNF-alpha, IL-1alpha (examples 4 and 5) Administering human or viral IL-10 to cultured human monocytes inhibited TNF-alpha, GM-CSF, IL-1alpha and IL-6 production (examples 8, 10 and 11) Human IL-10 downregulates expression of class II MHC molecules on human monocytes (example 16) Human IL-10 protects mice against septic or toxic shock (examples 24-26)	Treatment of human PBMCs with rhCMV IL-10 inhibited the synthesis of IFN-gamma (example 4) and the synthesis of TNF-alpha (example 6) Administering rhCMV IL-10 to human monocytes inhibited the synthesis of TNF-alpha (example 8), GM-CSF (example 10), IL-1alpha (example 12) and IL-6 (example 14) Treatment of human monocytes with rhCMV IL-10 reduces the surface expression of classical Class I and Class II MHC molecules (examples 15 and 16) Examples 36-39 describe how related murine studies would be conducted using rhCMV IL-10

This chart thus illustrates that U.S. Patents have been granted on treatment methods using human IL-10 based, at least in part, on in vitro experiments that are similar in both form and result to those described in the current application. It should be noted, moreover, that the claimed treatment methods in U.S. Patent 5,770,190 are supported *only by in vitro experimental results*; no animal model studies are presented. In view of the foregoing comparison, it thus follows that in vitro results of the type set forth in the current application

enable the current claims and reasonably correlate with the claimed in vivo methods since related results with similar experiments have been found sufficient to support issued patents. Said differently, the assertion in the Office Action that the in vitro results described in the application fail to correlate with in vivo methods is at odds with issuance of U.S. Patents based upon similar in vitro results.

Third, that human IL-10 was initially shown to have promise in treating various immune and inflammatory diseases based upon in vitro trials similar to those described in the current application and then entered into clinical trials supports the conclusion that the in vitro results in the current application correlate with the presently claimed in vivo methods, particularly since the standard to enter clinical trials exceeds that required to satisfy the requirements of 35 U.S.C. 112, first paragraph. The MPEP, for instance, states that the initiation of clinical trials with respect to a therapeutic product or process means that Office personnel should presume that the subject matter of a trial is reasonably predictive of having the asserted utility (see, e.g., MPEP 2107.03). This is because:

> Before a drug can enter human clinical trials, the sponsor, often the applicant must provide a convincing rationale to those especially skilled in the art (e.g., the Food and Drug Administration) that the investigation may be successful. Such a rationale would provide a basis for the sponsor's expectation that the investigation may be successful. In order to determine a protocol for phase I testing, the first phase of clinical investigation, some credible rationale of how the drug might be effective or could be effective would be necessary. (MPEP 2107.03; emphasis in original).

So the fact that a drug candidate has simply *entered* clinical trials is in itself evidence that those *especially* skilled in the art deem there to be credible evidence that the compound will have the efficacy that is claimed.

In the case of human IL-10, in vitro results of the kind described in U.S. Patent Nos. 5,770,190 and 5,883,976 indicated that human IL-10 could be effective in the treatment of various diseases. Various animal trials and clinical trials using human IL-10 to treat a number of different diseases were subsequently undertaken in view of promising in vitro results (see table

below). Since the requirements for entering a clinical trial exceed those for establishing enablement, it thus follows that the in vitro results with human IL-10 reasonably correlate with in vivo methods. Since, as described above, the current application describes a number of in vitro results with rhCMV IL-10 that are related both in terms of experimental protocol and outcome with certain in vitro methods conducted with human IL-10 (e.g., U.S. Patent Nos. 5,770,190 and 5,883,976), it thus also follows that these in vitro results reasonably correlate with in vivo treatment methods. So for this reason also, it is submitted that the in vitro experiments correlate with the claimed in vivo methods, and that these experiments, together with other guidance in the specification and the general knowledge in the art, sufficiently enable the presently claimed methods.

Disease	Exemplary References Discussing Animal Studies and Clinical Trials with human IL-10
Psoriasis	Moore et al. (2001) Annu. Rev. Immunol. 19:683-765, at 722 Asadullah, et al. (1998) J. Clin. Invest. 101:783-94 Asadullah, et al. (1999) Arch. Dermatol. 135:187-92 Friedrich, et al. (2002) J. Investig. Dermatol. 118:672-77
Hepatitis	Asadullah et al (2003) Pharmacological Reviews 55:241-269 at 260-261 Dharancy, C. (2000) Gastroenterology 119:1411-12 Nelson, et al. (2000) Gasteroenterology 118:655-660
Multiple sclerosis	Asadullah et al (2003) Pharmacological Reviews 55:241-269, see, e.g., pages 253-54
Asthma	Asadullah et al (2003) Pharmacological Reviews 55:241-269, see e.g., pages 254-55
Endotoxic and septic shock	Opal, et al. (1998) Clinical Infectious Disease 27:1497-1507 at page 1498 and 1501 van der Poll et al. (1995) J. Immunol. 155:5397-5401

Ulcerative colitis	Opal, et al. (1998) Clinical Infectious Disease 27:1497-1507 at page 1498 and 1504 Opal and Cross (1997) Sepsis 1:55-60
Inflammatory bowel disease	Steinhart, et al. (2001) Can. J. Gastroenterol. 15:799-804 Dejaco, et al. (2000) J. Invest. Medicine 48:449-456
Crohn's disease	Fedorak et al. (2000) Gastroenterology 119: 1473-1482 Schreiber et al. (2000) Gastroenterology 119:1461-1472 Tilg, et al. (2002) Gut 50:191-195
Rheumatoid arthritis	Moore et al. (2001) Annu. Rev. Immunol. 19:683-765 at 710 and 721 Asadullah et al. (2003) Pharmacological Reviews 55:241-269 at page 253 and 258 Keystone, et al. (1998) Rheum. Dis. Clin. North Am. 24:629-39
Graft Rejection/Graft-vs-Host Disease	Moore et al. (2001) Annu. Rev. Immunol. 19:683-765, see e.g., pages 717-718 Wissing, et al. (1997) Transplantation 64:999-1006
Allergic Responses	Moore et al. (2001) Annu. Rev. Immunol. 19:683-765, see, e.g., pages 711-712

The second enablement concern expressed in the Office Action is that the specification does not provide sufficient teaching as to how it can be assessed that treatment was achieved. Applicants disagree for two major reasons. First, symptoms associated with various immune diseases are known in the art and, as extensively described in the prior response, the specification provides considerable detail on specific symptoms associated with a large number of diverse immune disorders. One of skill would know that one option for monitoring the effectiveness of a treatment would be to monitor whether the treatment ameliorated one or more of the symptoms associated with the particular disease being treated. Secondly, a number of animal studies and clinical trials listed in the table above were commenced prior to the priority date of the current application. That the efficacy of human IL-10 was investigated with respect

to a wide variety of immune diseases and other disorders demonstrates that those of skill knew how to evaluate the efficacy of treatment of such diseases.

The third enablement issue raised in the Office Action is the contention that the specification does not enable prophylactic treatment methods. The Office Action raises two specific concerns in this respect. It is first stated that the burden of enablement is increased for prophylactic methods "due to the need to *screen* those human susceptible to such diseases" and that "the specification does not provide guidance as to how one skilled in the art would go about *screening* those patients susceptible to an immune disorder or an inflammatory response" (Office Action, at page 5, second full paragraph). Applicants interpreted similar language, particularly the references to "screening" in the last response to mean that the Examiner is of the view that those of skill in the art are incapable of identifying those that could potentially benefit from prophylactic treatment. The Office Action, however, states without explanation that this is not the issue. If by the word "screening" the Examiner means something besides identifying those individuals that could benefit from prophylactic treatment, then Applicants request clarification.

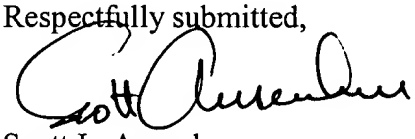
If, however, the assertion is in fact that those of skill would not have known how to identify those that could benefit from prophylactic treatment, then applicants disagree. As pointed out in the last response, individuals susceptible to a number of immune disorders can be identified, for instance, based upon upcoming events in the individual's life that put them at risk (e.g., a medical procedure), past events that put the individual at risk (known exposure to a pathogen which can induce an immune disorder in an infected individual), genetic susceptibility, clinical history and risk factors associated with life style. Applicants also included a chart in the last response that listed exemplary approaches that could be utilized to identify individuals that could benefit from prophylactic treatment for a number of different disorders.

The second specific issue is again the assertion that the specification lacks adequate guidance on whether a treatment protocol has been effective. The response to this is the same as that set forth above, namely that based upon general knowledge in the art and the teachings in the specification that one of skill would have known what symptoms are associated with various disorders and that one approach for monitoring efficiency would be to monitor the patient to determine whether the symptom was ameliorated. That such approaches were know is

evidenced, in part, by the fact that a number of clinical trials with respect to immune and inflammatory diseases were conducted prior to the priority date of the instant application.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 303-571-4000.

Respectfully submitted,



Scott L. Ausenhus
Reg. No. 42,271

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 303-571-4000
Fax: 415-576-0300
Attachments
SLA:nmb
60233375 v1